



FLAG vs FLAG-IDA: outcomes in relapsed/refractory acute leukemias

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Abstract

Background FLAG (fludarabine, cytarabine, granulocyte colony—stimulating factor) and FLAG-IDA (idarubicin added to standard FLAG) are salvage chemotherapy regimens used for relapsed and refractory acute leukemias. The toxicity of the FLAG-IDA courses is generally more severe than for the FLAG courses, with marked neutropenia and thrombocytopenia. This study aims to compare the outcomes of both regimens in terms of morbidity, mortality and remission/transplant. No comparison has been reported so far in Pakistan or the rest of third world countries.

Methodology This retrospective study was conducted in Hematology and Bone Marrow Transplant unit after approval from Institutional Review Board and Ethics Committee. 76 leukemic patients treated with salvage chemotherapy were included. Our endpoints for patient outcome analysis included disease remission/relapse, HSCT following remission, morbidity, mortality, progression free survival and overall survival. Kaplan Meier curves were made in SPSS for survival analysis.

Results A total of 76 patients were included from 2015 to July 2018. 49 patients were given FLAG, and 27 were given FLAG-IDA. 31.6% in FLAG-IDA achieved complete remission (CR)/complete remission with incomplete counts (CRi). 21% in FLAG-IDA made it to Bone marrow transplant (BMT) (67% of those in CR/CRi). 41.7% in FLAG achieved CR/CRi, and 27.8% in FLAG made it to BMT (67% of those in CR/CRi). Common complications in both regimens were infection, bleeding and other complications e.g., rash, diarrhea, mucositis, etc. A statistically significant difference was found between overall survival of the two regimens, *p* value 0.033.

Conclusions FLAG regimen was found superior to FLAG-IDA with better survival and subsequent transplant rate.

Keywords FLAG · FLAG-IDA · BMT · AML · ALL

Relapsed/refractory acute leukemias are associated with poor prognosis and lower survival rates [1, 2]. Allogeneic hematopoietic stem cell transplant (HSCT) is currently the only widely available option in most regions of the world for providing most favorable outcome in these patients.

FLAG (fludarabine, high dose cytarabine-arabinofuransyl cytidine, or ara-C, Granulocyte colony—stimulating factor) is a non-anthracycline-based regimen used for relapsed and refractory acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). An anthracycline Idarubicin is sometimes added to standard FLAG protocol to improve outcome with an increased antileukemic action, less

susceptibility to multidrug resistance and less cardiotoxicity compared to other anthracyclines [3].

Although single centered studies present varied results, FLAG-IDA toxicity was found more severe with marked neutropenia and thrombocytopenia, compared to FLAG courses in a phase II trial [4]. In our center, we retrospectively analyzed the outcomes of FLAG with and without Idarubicin to evaluate the better treatment protocol that can effectively serve as bridge to HSCT. To the best of our knowledge, no comparison has been reported so far from Pakistan or the rest of third world countries.

This study was conducted in Hematology and Bone Marrow Transplant unit after approval from Institutional Review Board and Ethics Committee. 76 leukemic patients treated with salvage chemotherapy between 2015 and July 2018 were included. Our endpoints for patient outcome analysis included disease remission/relapse, HSCT following remission, morbidity, mortality, progression free survival (PFS) and overall survival (OS). We calculated PFS from the 1st

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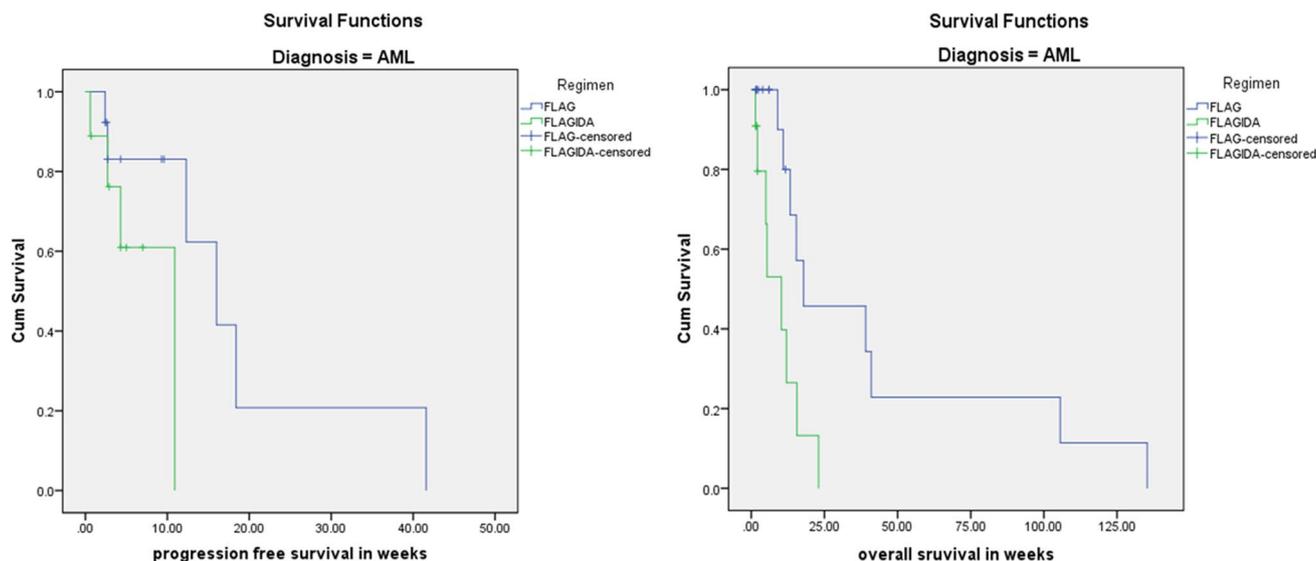


Fig. 1 Kaplan–Meier curves for AML: FLAG vs FLAG-IDA

day of salvage regimen to the last day patient was still in remission. OS was calculated till the day of last follow-up.

Patients with less than 5% blasts on bone marrow biopsy were said to be in complete remission (CR). Those who did not recover peripheral counts (WBC < 5000/ μ l or platelet count < 20,000/ μ l) with less than 5% blasts and hypocellularity on bone marrow aspirate were said to be in complete remission with incomplete count recovery (CRi).

We defined regimen associated mortality (REM) as mortality occurring within the first 30 days of cycle completion due to causes unrelated to the underlying disease. OS and PFS of both regimens were calculated using the Kaplan Meier curves in SPSS, and log rank test was used to evaluate the differences between the curves. Kaplan Meier curves were also made to compare OS and PFS between AML and ALL patients.

Forty-nine patients aged 4–71 years (mean 28.4) with acute lymphoblastic leukemia ($n=23$), acute myeloid leukemia ($n=22$), chronic myeloid leukemia blast crisis ($n=2$), biphenotypic leukemia ($n=1$), promyelocytic leukemia ($n=1$) were treated with FLAG regimen (day 1–5). 15/36 patients (41.7%) achieved complete remission (30.6% CR and 11.1% CRi), while 21/36 patients (58.3%) were not in remission. 10/36 patients (27.8%) underwent successful bone marrow transplant (67% of those in CR/CRi). Data of 13 patients treated with FLAG was not documented.

Twenty-seven patients aged 13–53 years (mean 27.8) with acute myeloid leukemia ($n=15$), acute lymphoblastic leukemia ($n=11$), CML blast crisis ($n=1$) were treated

with FLAG-IDA (day 1–5). 2/19 patients (10.5%) achieved complete remission, 4/19 (21.1%) achieved complete remission with incomplete counts while 13/19 (68.4%) were not in remission. 4/19 patients (21.1%) made it to bone marrow transplant successfully. (67% of those in CR/CRi). Data of 8 patients treated with FLAG-IDA was not documented.

Regimen associated mortality was 37.5% for FLAG vs 57.1% for FLAG-IDA. Main cause of mortality was sepsis for both treatments. Common morbidities post FLAG cycle included bleeding, infection, diarrhea and mucositis. Most common complication encountered post FLAG-IDA cycle was neutropenic fever.

The OS at a follow-up of 25 weeks was 45% for FLAG vs 20% for FLAG-IDA. Average follow-up time of patients was 18 weeks (range: 1–136 weeks). A statistically significant difference was found between overall survivals of the two regimens, p value 0.033. Excluding 5 patients from the total 76, (3 CML blast crisis, 1 promyelocytic leukemia, 1 biphenotypic leukemia), FLAG in AML patients appeared as the better regimen in terms of overall survival, p value 0.007 (Fig. 1). There was no significant difference between outcomes of both treatments in ALL patients (Fig. 2). 6/34 (17.6%) patients with ALL transitioned to transplant, compared to 7/37 (18.9%) patients with AML (Fig. 3).

From our center experience, we found FLAG regimen superior to FLAG-IDA with better survival and subsequent transplant rate.

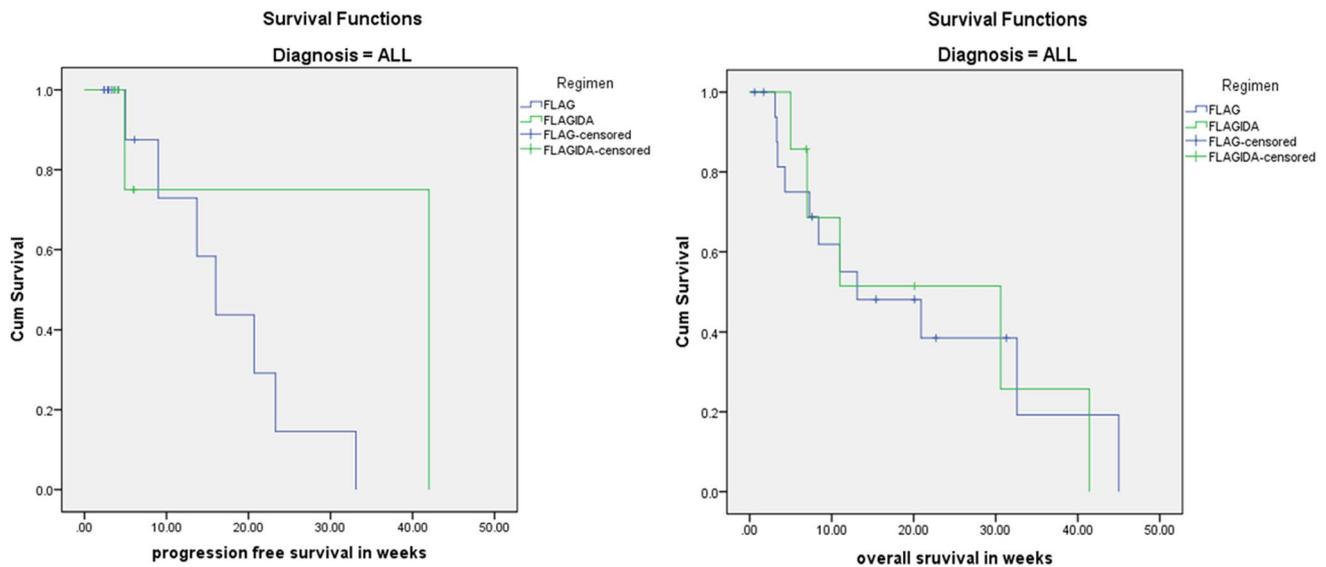
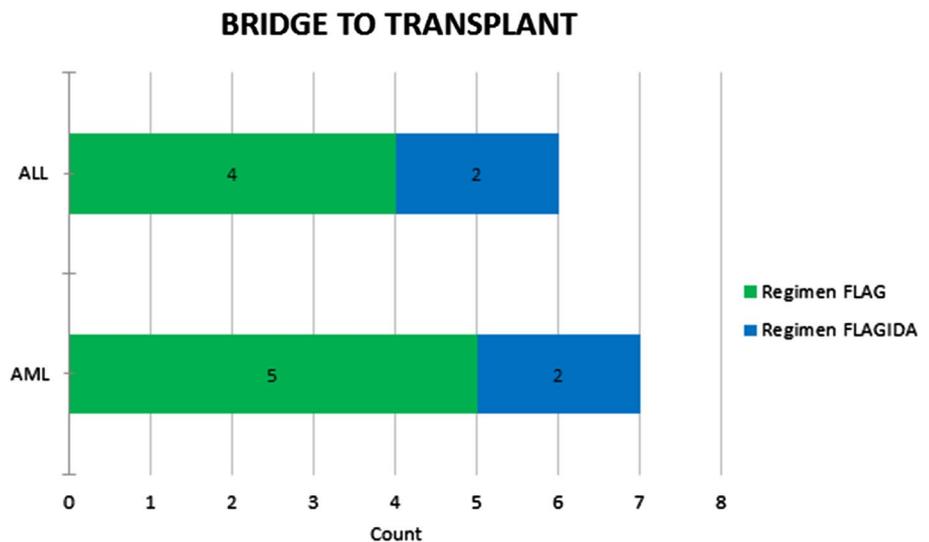


Fig. 2 Kaplan–Meier curves for ALL: FLAG vs FLAG-IDA

Fig. 3 Number of patients who proceeded to HSCT post chemotherapy



Author contributions MAM: corresponding author, study concept and design, revising the intellectual content; MUF: manuscript writing, analysis/data interpretation, data collection; FM: data collection; DHK: biostats, data analysis; AF: data collection.

Compliance with ethical standards

Conflict of interest No financial conflict of interest to report by an author.

References

1. Ramos NR, Mo CC, Karp JE et al (2015) Current approaches in the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Med* 4:665–695

2. Einsiedel HG, von Stackelberg A, Hartmann R et al (2005) Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. *J Clin Oncol* 23:7942–7950

3. Parker JE, Pagliuca A, Mijovic A et al (1997) Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukemia. *Br J Haematol* 99:939–944

4. Fleischhack G, Hasan C, Graf N et al (1998) IDA-FLAG (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experiences of a phase II trial. *Br J Haematol* 102:647–655

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